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Impaired left ventricular filling rate induced by treatment with recombinant interleukin 2 for advanced cancer

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Abstract

***Background*—Immunotherapy with recombinant interleukin 2 (rIL 2) has been extensively used to treat cancer but its use has been hampered by serious side effects including severe hypotension, arrhythmias, and myocardial infarction.**

***Objective*—To assess the effects of rIL 2 on human left ventricular function.**

***Methods*—Left ventricular (LV) function was monitored in 22 patients (9 women, 13 men) (mean (SD) age 53 (10) years) undergoing a 120 h continuous intravenous infusion of rIL 2 (18×10^6 IU/m²/day) for melanoma (4), renal cell (16), ovarian (1), and colon cancer (1). Radionuclide ventriculography was performed before and 1 h after the end of treatment. Ejection fraction (EF), peak emptying rate (PER), peak filling rate (PFR), and regional left ventricular wall motion were analysed. Heart rate (HR), central venous pressure (CVP), systolic (SBP) and diastolic blood pressures (DBP), the electrocardiogram, and myocardial enzyme concentrations were monitored throughout the study.**

***Results*—All variables (mean (SD)) were normal before rIL 2 was given. After rIL 2 administration HR increased significantly from 84 (11) to 125 (18) beats/min ($p < 0.0001$), SBP fell from 128 (11) to 100 (9) mm Hg ($p < 0.001$) and DBP from 76 (9) to 65 (7) mm Hg ($p < 0.0001$). CVP decreased from 3·70 (3·2) to 1·30 (0·45) cm H_2O ($p < 0.001$). EF (65 (7) to 64 (8%) and PER (3·56 (0·60) to 3·86 (0·83) EDV/s) did not change significantly. PFR decreased significantly at the end of the rIL 2 infusion from 2·68 (0·46) to 2·37 (0·43) EDV/s ($p < 0.01$). Left ventricular segmental hypokinesia developed in 6 patients. Myocardial enzyme concentrations remained normal throughout the study.**

***Conclusions*—The results of this study confirmed that rIL 2 produces important haemodynamic changes, predominantly related to decreased systemic resistance. However, the observed reduction in PFR in most patients suggested that rIL 2 might exert its action at the level of the heart muscle itself. The localised systolic dysfunction in some patients suggested that rIL 2 might also adversely affect myocardial perfusion.**

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Recombinant interleukin 2 (rIL 2) has been extensively used, both alone and in association with lymphokine-activated killer cells, to treat malignant neoplasms, such as renal cell carcinoma and melanoma.[1]

rIL 2 commonly causes cardiovascular side effects. Almost all clinical trials of rIL 2 have reported important complications such as tachycardia and hypotension,[3,4] fluid retention,[5] myocardial infarction,[6,7] myocarditis,[8] complete heart block,[9] and a decrease in ejection fraction.[10]

Although the mechanisms responsible for the cardiovascular effects of rIL 2 are largely unknown, a recent study suggested a partial relation with a decrease in peripheral vascular resistance, resembling the early phase of septic shock.[11] The cardiovascular collapse associated with septic shock is largely caused by bacterial endotoxin,[12] which is known to stimulate the synthesis and release of different cytokines and biological mediators with hypotensive activity including tumour necrosis factor (TNF). Hesse *et al*[13] and Beutler *et al*[14] proposed that TNF contributed to the cardiovascular collapse of septic shock by releasing secondary mediators such as endothelium-derived relaxing factor (EDRF), a hypotensive agent,[15] which accounts for the cardiovascular changes associated with endotoxin and cytokine administration.[16,17] There is experimental evidence that human monocytes stimulated with rIL 2 release a soluble factor that severely impairs myocardial function.[18]

To determine whether the haemodynamic changes during rIL 2 therapy were also related to a cardiotoxic effect we studied ventricular function in 22 patients with advanced metastic cancer undergoing continuous intravenous infusion of rIL 2.

Patients and methods

PATIENTS

From January 1990 to January 1992 rIL 2 therapy was considered for 73 patients with cancer (kidney (66), melanoma (five), colonic cancer (one), and carcinoma of the ovary (one). Table 1 lists the exclusion criteria in 51 patients. Eventually we treated 22 patients with rIL 2 (16 with renal cell carcinoma, four with melanoma, one with epithelial ovarian cancer, and one with colon cancer). They were 13 men and nine women (mean (SD) age 53 (10) years). All had measurable disease (Karnofsky Performance Status > 80). None had obvious contraindications to rIL 2

Table 1 Exclusion criteria

Exclusion criteria	*No of patients*
Age > 80 yr	3
Poor performance status	15
Cardiac disease	6
Cerebral metastases	7
Positive hepatitis markers	3
Previous rIL 2 treatment	9
Kidney failure	2
Liver failure	1
Severe diabetes mellitus	1
Vena cava thrombosis	1
Clotting deficiency	1
Second neoplasm	1
Patient refusal	1

therapy or had been given chemotherapy, radiotherapy, or immunotherapy. None had clinical (history and physical examination) or laboratory (electrocardiogram, chest *x* ray, cross sectional echocardiogram) evidence of cardiac disease. All gave written informed consent before treatment with rIL 2.

Recombinant IL 2 (EuroCetus, Amsterdam, The Netherlands) was given intravenously by continuous infusion through a central venous catheter at a dose of 18×10^6 IU/m²/day for 120 consecutive hours, according a standardised protocol for our hospital.

CLINICAL, ECG, AND PHYSIOLOGICAL DATA

The patients' clinical condition was closely monitored throughout rIL 2 administration. Serial measurements of central venous pressure, arterial blood pressure (cuff sphygmomanometer), and heart rate (two lead ECG monitor) were obtained at baseline and every 4 h during rIL 2 treatment. The 12 lead ECG and cardiac enzyme determinations were obtained daily, before, during and up to 3 days after treatment.

RADIONUCLIDE VENTRICULOGRAPHY

Equilibrium radionuclide ventriculography was performed before and less than 1 h after the end of rIL 2 infusion. The blood pool was labelled in vivo by intravenous injection of 18 μg/kg of stannous pyrophosphate followed, after 20–30 minutes, by 555 MBq (15 mCi) of ^{99m}Tc pertechnetate. A gamma camera with a small field of view and equipped with a low energy general purpose collimator was positioned over the chest in the best left anterior oblique position (45° with a 10° craniocaudal angulation) for imaging the septum. Radionuclide data were analysed after time and spatial image smoothing. We excluded frames with total counts that were less than 95% of the end diastolic image. Parametric data were assessed both qualitatively and quantitatively.

Qualitative patterns of left ventricular shape and segmental wall motion (five segments: anterior, septal, inferior, apical, lateral) were analysed by continuous cineloop display of smoothed images and display of a group of parametric images (phase, amplitude, stroke volume and ejection fraction). The presence of abnormal segmental contractility was assessed and graded by two independent observers. When it was present, cross sectional follow up echocardiography was repeatedly performed to check on its reversibility. The latter technique was preferred to radionuclide ventriculography because it avoided further radiation exposure. Total whole body radiation exposure was approximately 5·7 mGy (0·57 rad).

Left ventricular peak filling (PFR) and emptying rates (PER) were separately assessed by fitting a third order polynomial function of the left ventricular time/activity curve by a least-squares technique. The peak filling and emptying rates were computed in left ventricular counts per second, normalised for the number of counts at end diastole, and expressed as end diastolic counts per second (EDV/s). This approach does not imply knowledge of actual left ventricular end diastolic volume.

Global ejection fraction was also calculated from the left ventricular time/activity curve.

STATISTICAL ANALYSIS

All group data are reported as mean (SD). Data from the scintigraphic studies were analysed by a two-tailed Student's *t* test for paired data. A value of $p < 0.05$ was regarded as significant.

Results

CLINICAL, ECG, AND PHYSIOLOGICAL DATA

During the first 48 hours of rIL 2 infusion all patients experienced fever, chills, and malaise. Their body weight increased from 65·2(14·3) to 66·4(14·3) kg ($p = 0.007$). They all developed mild hypotension with compensatory tachycardia, but none required vasopressor drugs or rapid fluid replacement. Heart rate increased from 84(11) to 125(18) beats/min ($p < 0.0001$), and systolic and diastolic blood pressure decreased from 128(11) to 100(9) and from 76(9) to 65(7) mm Hg, respectively ($p < 0.0001$ for both) (fig 1). Both heart rate and blood pressure returned to preinfusion values between 4 and 24 h from the end of infusion. Central venous pressure decreased from 3·7(3·2) to 1·3(0·45) cm H_2O ($p < 0.001$). Nine patients developed T wave inversion in leads V2-V4 which also normalised within 24 hours; one patient had frequent supraventricular and ventricular extrasystoles and on the fourth day of infusion another developed paroxysmal atrial fibrillation that spontaneously reverted to sinus rhythm after 3 h. Cardiac enzymes remained within the normal range throughout the study.

RADIONUCLIDE VENTRICULOGRAPHY

Before rIL 2 therapy, regional wall motion and all quantitative indices of global ventricular function were within the normal reference values for our laboratory. Immediately after the end of rIL 2 therapy the peak emptying rate increased from 3·56(0·60) to 3·86(0·83)

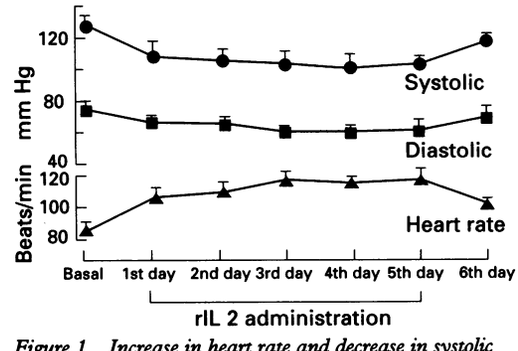

Figure 1 Increase in heart rate and decrease in systolic and diastolic blood pressure (mean (SD)) during rIL 2 administration. These variables returned to basal values within 24 hours of drug withdrawal.

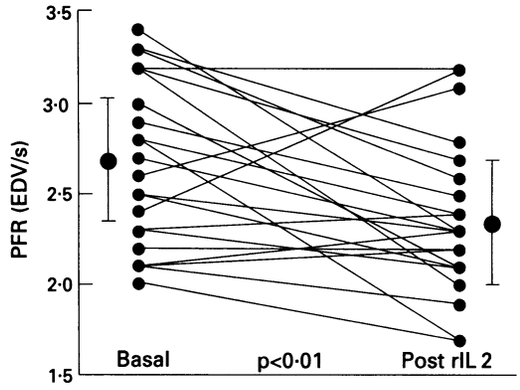

Figure 2 Individual left ventricular peak filling rate (PFR) before and soon after rIL 2 infusion.

EDV/s (NS) and the ejection fraction decreased from 65(7)% to 64(8)% (NS).

The peak filling rate decreased significantly from 2·68(0·46) to 2·37(0·43) EDV/s ($p < 0·01$) (fig 2) after rIL 2. Localised hypokinesia developed in eight myocardial segments in six patients: two of these patients also developed transient repolarisation abnormalities on the surface ECG. In this subgroup all quantitative indices of left ventricular function deteriorated with rIL 2 therapy: PFR decreased from 2·63(0·48) to 2·10(0·33) EDV/s ($p = 0·0092$), PER from 3·65(0·63) to 3·01(0·69) EDV/s ($p = 0·02$), and EF from 62(7)% to 56(8)% ($p = 0·04$). Cross sectional follow up echocardiography performed within 7 days of the end of rIL 2 administration, invariably showed normalisation of the previously hypocontractile segments. We could find no difference related to age, sex, coronary risk factors, and changes in heart rate and blood pressure induced by rIL 2 to explain the variable behaviour of global and regional left ventricular function in individual patients. Table 2 shows individual clinical and radionuclide data.

Discussion

The results of our study confirm that intravenous administration of rIL 2 causes important haemodynamic changes characterised by a decrease in both systolic and diastolic blood pressure associated with an increase in heart rate. This haemodynamic pattern resembles that of the early phase of septic shock, where the development of severe hypotension and the compensatory increase in heart rate are caused by profound reduction in systemic vascular resistance.[16] A cytokine-induced increase in NO synthesis is now recognised to account for most of the cardiovascular changes associated with rIL-2 administration[14 15] and indeed in vitro exposure of vascular tissue to cytokines impaired the response to vasoconstrictor agents[19] associated with the appearance of inducible NO synthase in the tissue preparation. These changes can be reversed or prevented by NO synthase inhibitors[20] that also revert the hypotension induced by TNF or lipopolysaccharide administration in both dogs and rats.[15 21] Therefore, induction of NO synthase in the vessel wall by sepsis or cytokines or both is likely to be responsible for the hypotension and attenuation of vascular responses to pressor agents.[22 23] The increase in plasma concentrations of NO 2 and NO 3 in patients with advanced cancer who develop hypotension during rIL 2 immunotherapy accords with this suggestion.[24]

Data from other published reports and the results of our study support the idea that rIL 2 can impair left ventricular function by various mechanisms. Cytokine-induced inhibition of the accumulation of cyclic AMP stimulated by β adrenergic agonists, caused by disruption of signal transduction across the sarcolemma, has been shown to blunt cardiac myocyte contractility.[25 26]

In our study the left ventricular peak filling rate, a sensitive index of diastolic function,

Table 2 Clinical and radionuclide data in 22 patients treated with rIL 2.

				HR (beats/min)		Time to HR D-Max	BP (mm Hg)		Time to BP D-Max	EF (%)		PFR (EDV/s)		PER (EDV/s)		LV function	ECG
Patient	Age	Sex	Ca site	Pre	D-Max	(h)	Pre	D-Max	(h)	Pre	Post	Pre	Post	Pre	Post	post	post
1	50	M	Kidney	76	113	112	135/90	95/55	88	62	68	2·6	3·1	3·6	4·1	Normal	T V2 and 4
2	45	F	Melanoma	84	140	60	130/80	90/60	83	63	54	3·4	2·3	3·9	2·3	Hyp apex	Normal
3	45	M	Kidney	88	123	30	130/90	110/60	114	71	58	2·8	2·4	3·6	3·2	Hyp sept	Normal
4	50	M	Kidney	92	109	58	125/80	110/65	18	59	63	2·4	3·2	2·9	4·0	Normal	Normal
5	43	M	Kidney	97	145	118	135/85	110/80	87	57	49	2·3	2·4	3·2	2·6	Hyp sept-apex	T V2 and 3
6	47	M	Kidney	89	180	5	130/70	105/75	18	50	50	2·1	1·9	2·9	2·8	Normal	T V2 and 3
7	49	F	Ovary	104	132	60	120/70	100/65	6	67	61	2·5	2·3	2·8	4·2	Normal	Normal
8	58	M	Melanoma	77	120	104	110/90	100/75	3	61	63	2·1	2·2	3·5	3·8	Normal	T V3 and 6
9	44	M	Melanoma	75	135	44	135/75	110/70	46	55	53	2·8	1·7	3·3	3·0	Hyp sept-apex	Normal
10	59	M	Melanoma	94	140	92	110/70	90/60	83	60	60	2·9	2·5	4·8	4·1	Normal	Normal
11	64	M	Melanoma	92	140	98	140/85	110/60	115	56	53	2·8	1·7	3·1	3·0	Hyp sept	PAF
12	63	F	Melanoma	76	110	32	120/75	80/55	71	79	79	2·3	2·1	4·6	5·5	Normal	T V2 and 3
13	53	F	Melanoma	90	130	118	130/70	105/65	69	68	71	3·2	2·7	3·2	4·4	Normal	T V2 and 3
14	68	M	Melanoma	75	111	52	140/90	110/70	5	67	71	2·5	2·1	4·8	4·3	Hyp sept	T V2 and 4
15	60	F	Colon	75	113	9	130/65	105/60	13	65	65	2·1	2·3	3·6	3·2	Normal	Normal
16	73	F	Kidney	89	106	87	155/70	100/70	70	70	71	3·0	2·1	3·5	4·2	Normal	T V2 and 3
17	73	M	Kidney	79	110	57	125/80	100/70	51	65	69	2·2	2·2	3·7	3·1	Normal	Normal
18	35	F	Melanoma	104	134	67	110/65	90/70	36	66	63	3·2	2·0	3·1	4·9	Normal	T V5 and 6
19	65	F	Kidney	78	108	98	140/75	100/60	42	75	71	3·3	2·6	4·2	5·0	Normal	Normal
20	39	M	Kidney	88	128	93	130/70	105/70	23	67	65	3·3	2·8	3·9	4·0	Normal	Normal
21	44	M	Kidney	67	130	28	115/65	85/55	26	75	67	2·8	2·4	3·8	4·0	Normal	T V2 and 4
22	56	F	Melanoma	58	96	98	140/85	110/60	115	73	76	3·2	3·2	3·0	4·8	Normal	T V2 and 3

BP, blood pressure; Ca, cancer; D-Max, maximal variation in HR and BP; EF, ejection fraction; HR, heart rate; hyp, hypokinesia; LV, left ventricular; PAF, paroxysmal atrial fibrillation; PER, peak emptying rate; PFR, peak filling rate; Pre, pre r-IL2 infusion; Post, post r-IL2 infusion; sept, septum; T, T wave inversion; Time, interval between start of infusion and maximal variation in heart rate and blood pressure.

was significantly reduced during rIL 2 infusion in most of the 22 patients and often in the absence of a concomitant impairment of systolic function, suggesting a primary effect on the diastolic properties of the myocardium, possibly induced by transient interstitial oedema. Indeed, in all our patients body weight increased after rIL 2, probably because of fluid retention.[5] An earlier study showed that myocardial oedema may cause compliance to decrease without affecting myocardial contractility.[27]

The major determinants of the atrioventricular pressure difference during early diastole are the rate and duration of ventricular relaxation, passive ventricular compliance, the end systolic volume, the compliance of the atrium, and the atrial pressure at the onset of atrioventricular valve inflow.[28] Therefore, among other factors, the modest but significant decrease in central venous pressure seen in our patients might also have contributed to a reduction in diastolic filling rate through a decrease in atrial filling pressure.

In six patients localised systolic wall motion was impaired immediately after rIL 2 administration. In all cases the hypokinesia affected the anteroseptal wall and was associated with reduction in peak emptying and filling rates and ejection fraction. Although these changes were associated with ST-T alterations in only two patients they resemble the pattern of left ventricular function impairment seen during ischaemia.[29 30] This suggests the possibility that in some patients with latent coronary artery disease rIL-2 may reduce regional coronary flow and hence cause myocardial ischaemia and regional wall motion abnormalities. Clinical studies are needed to assess changes in myocardial perfusion after in vivo rIL 2 administration.

CLINICAL IMPLICATIONS

Treatment with rIL 2 always induced significant haemodynamic changes, including a decrease in arterial pressure and a compensatory increase in heart rate. In addition, some patients developed variable degrees of reversible left ventricular dysfunction. When careful attention is paid to fluid status and blood pressure support patients can be safely managed through the haemodynamic toxicity of this therapy. However, in patients with cancer and with known or suspected coronary disease, the possibility that rIL 2 cytokine-induced deterioration of their cardiac condition should be taken into account.

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